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TITLE

PRODRUGS AND CONJUGATES OF THIOL- AND SELENOL-
CONTAINING COMPOUNDS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

5 This application is a continuation of United States Patent No. 6,340,746 B1,
Application No. 09/485321, filed July 20, 2002, titled "PRODRUGS AND
CONJUGATES OF THIOL- AND SELENOL-CONTAINING COMPOUNDS AND
METHODS OF USE THEREOF" nationalized from PCT/US98/16324, filed August 6,
1998, which claimed priority to United States Provisional Patent Application 60/055,019,
10 filed August 7, 1997 (which applications are hereby incorporated by reference).

FIELD OF THE INVENTION

 The present invention relates to sulfur- and selenium-containing compounds and
methods for using these compounds to protect mammals from toxic insults. More
specifically, the present invention relates to prodrugs and conjugates of thiol- or selenol-
15 containing compounds, such as cysteine, cysteamine, glutathione, selenocysteine,
selenocysteamine, and the Walter Reed (WR) compounds.

BACKGROUND OF THE INVENTION

Technical Background

 Thiol- or selenol-containing compounds, e.g., cysteine, cysteamine, glutathione,
20 selenocysteine, selenocysteamine, and the WR compounds, are known protective and
preventive agents. Potential protective or preventive uses of such agents are widespread,
as in reducing the unwanted side effects of chemo- or radiotherapy of cancer, improving
cardiovascular function, preventing mutagenesis, preventing the initiation and/or
progression of cancer, reducing toxic consequences of planned or unplanned radiation or
25 chemical exposures, slowing the aging process, and preventing cataract formation. New

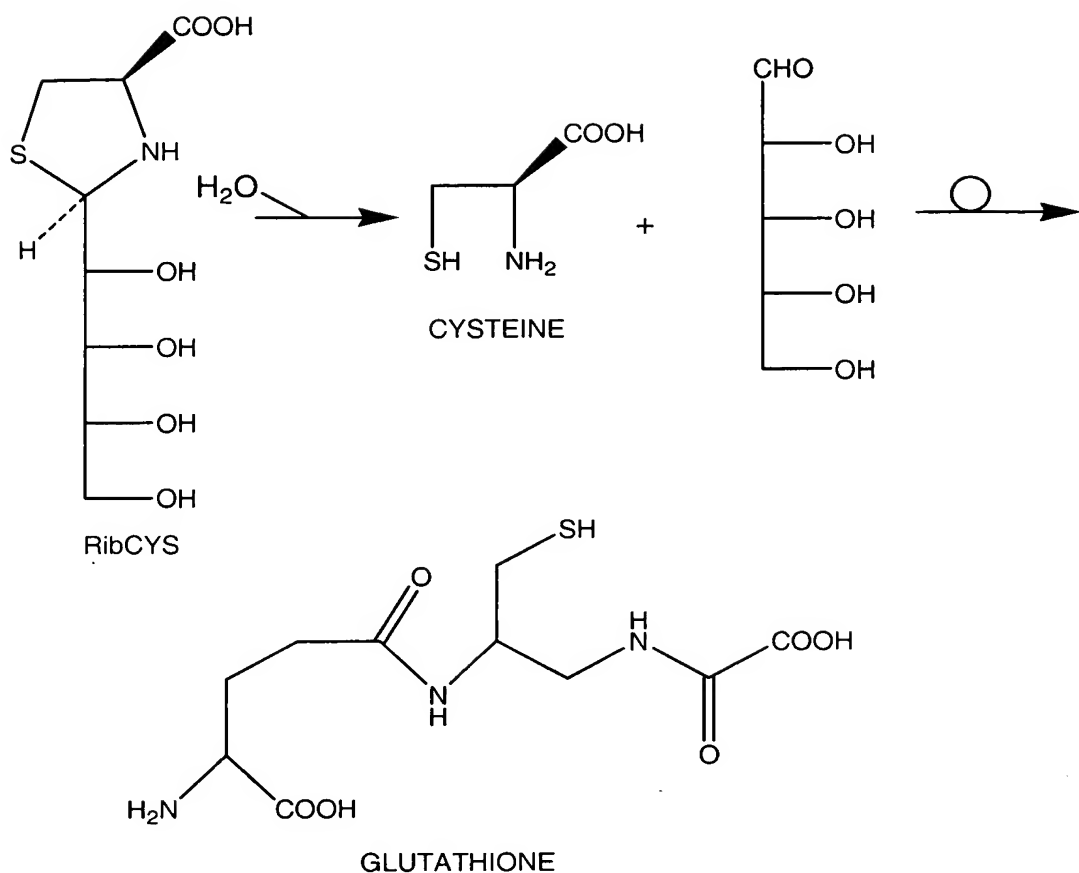
evidence also links these compounds to altered gene expression and enhanced cellular repair processes.

The activity of these thiol- or selenol-containing compounds is mainly due to the sulfur or selenium atom participating in nucleophilic attack on toxic electrophiles, scavenging free radicals, effecting repair of damaged targets through hydrogen atom donation, altering the redox status of the cell, or affecting gene transcription or protein function.

For example, the reduced form of glutathione (Glu-Cys-Gly), a naturally occurring tripeptide with a free sulfhydryl group (SH), serves as a sulfhydryl buffer that maintains the cysteine residues of hemoglobin and other proteins in a reduced state. Glutathione also plays a key role in detoxifying the body by reacting with both endogenous and exogenous compounds, such as hydrogen peroxide and other peroxides.

Evidence suggests that glutathione is useful at protecting the body from the harmful side effects of radiation and chemotherapy that often accompany cancer treatment. Cyclophosphamide (CTX), for example, is a widely used antitumor agent whose clinical utility is limited by its bladder toxicity. During CTX metabolism in the body, a compound, acrolein, is released. Acrolein is thought to be responsible for the urotoxicity of CTX. Glutathione has been implicated in CTX detoxification by conjugating to acrolein.

It has been of significant interest in the art, therefore, to increase glutathione synthesis especially during periods of toxic insults. L-Cysteine, a reactant in normal glutathione biosynthesis, is known to increase the synthesis of endogenous glutathione. To date, a significant challenge in the art has been to provide L-cysteine to cells at sufficiently high levels to drive glutathione biosynthesis. As disclosed, for example, in United States Patent 4,868,114 to Nagasawa et al., prodrugs of L-cysteine (i.e., chemical compounds converted to L-cysteine in the cell), such as RibCys, can be used by the cell to drive glutathione biosynthesis as shown below.



These prodrugs have been shown to offer good protection against a variety of toxic insults. However, the initial prodrugs are highly water soluble and are rapidly excreted by the body.

5 WR compounds are also of significant interest in the art. Over 4400 WR compounds were prepared and tested at the Walter Reed Army Hospital after World War II in an effort to develop radioprotective compounds that might be employed by military personnel during a nuclear encounter. The single agent with the greatest potential that arose from that extensive effort was WR-2721, which is converted to WR-1065 by
10 enzymatic cleavage. These compounds have several shortcomings, however, including that they possess noteworthy toxicity and little oral activity, greatly reducing their clinical utility.

Finally, selenocysteine is of significant interest in the art for its antioxidant and anticancer properties. In addition, selenium has received significant attention for its

ability to inhibit or delay the onset of AIDS caused by HIV infection. Selenium is also a cofactor of glutathione peroxidase, an enzyme which has been implicated in many detoxifying processes.

5 Selenium is an essential mineral that is critical to the normal functioning of many species, including humans. It also has demonstrated activity as a cancer chemopreventive agent. Selenium-containing compounds appear to have especially high preventive activity against the initiation phase of colorectal cancer, although its chemoprotective ability has been extended to cancers in many organs, caused by a variety of carcinogens.

10 To achieve this chemopreventive activity, levels of selenium at least five-fold greater than that required for normal nutritional status appear to be necessary. In addition, selenium must be given continuously for maximum inhibition. Unfortunately, selenium is also known for its profound toxicity, making selenium supplementation a distinct challenge.

15 Current selenium supplements rely on inorganic forms, such as sodium selenite (Na_2SeO_3) or sodium selenate (Na_2SeO_4). While these forms have some value, they are considered more toxic than necessary, and are unlikely to be useful in cancer chemoprevention. Several organoselenium compounds, which appear to be less toxic in general than the inorganic forms, have been proposed for in vivo use, but the full potential of this strategy has not yet been realized. In general, however, it is very clear
20 that the chemical form in which selenium is introduced consistently shows a marked influence on biological outcomes, including cancer chemoprevention and toxicity.

Selenocysteine is an organic form that is present in the body and is now recognized as the 21st amino acid used in protein synthesis. While it represents a valuable biochemical form, selenocysteine is chemically unstable and difficult to handle,
25 which has undoubtedly deterred its study and use. In addition, even though it possesses greatly reduced inherent toxicity, it still may be too toxic at chemopreventive doses to be therapeutically useful. Accordingly, prodrug forms of selenocysteine that possess reduced inherent toxicity and improved physicochemical properties would be desirable.

Objects of the Invention

It is, therefore, an object of the invention to provide prodrugs and conjugates of thiol- or selenol-containing compounds, such as cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and the WR compounds.

5 Another object of the invention is to provide such prodrugs of thiol- or selenol-containing compounds displaying reduced toxicity and increased clinical utility.

Another object of the invention is to provide such prodrugs of thiol- or selenol-containing compounds with increased lipophilicity that can target a specific organ or region of the body.

10 Another object of the invention is to provide such prodrugs of thiol- or selenol-containing compounds that can be conjugated to antioxidant vitamins, such as vitamin C and E, thus maximizing the effects by providing different agents that work by complementary mechanisms.

Further objects of the invention will become evident in the description below.

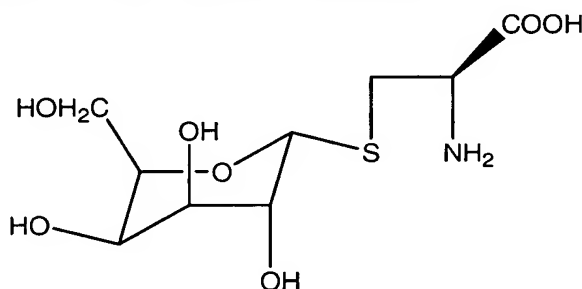
15 BRIEF SUMMARY OF THE INVENTION

The present invention is directed to novel prodrugs and conjugates of thiol- or selenol-containing compounds, including cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and the WR compounds. Potential protective or preventive uses of such agents are widespread, as in reducing the unwanted side effects of
20 chemo- or radiotherapy of cancer, improving cardiovascular function, preventing mutagenesis, preventing the initiation and/or progression of cancer, reducing toxic consequences of planned or unplanned radiation or chemical exposures, slowing the aging process, preventing cataract formation, etc.

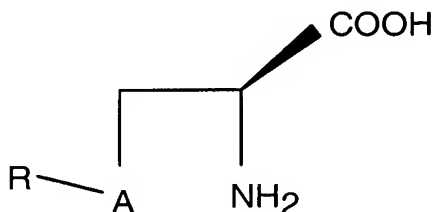
Prodrugs are inactive forms of a parent drug that have been created to overcome
25 one or more barriers to their effective use. In the present invention, prodrugs have been designed to overcome the chemical instability and/or possible toxicity barriers that exist with the parent drug.

In one embodiment, the invention relates to the design, synthesis, and evaluation of prodrugs of L-cysteine and L-selenocysteine, containing a thioglycoside or selenoglycoside on the free thiol or selenol. The protecting group will, in addition to protecting the thiol or selenol from oxidation, permit the targeting of specific sites within the body.

For example, the galactose protected cysteine shown below will target the liver and will enter the cytoplasm of hepatocytes. Delivering L-cysteine to hepatocytes has numerous uses, including protection against hepatotoxins, such as acetaminophen, and against side effects caused by local radiation treatments.



The cysteine/selenocysteine prodrugs can be depicted by the formula:

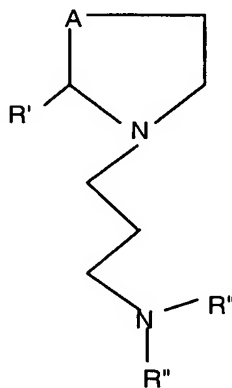


where A is a sulfur or a selenium, and R is derived from a mono-, di-, or oligo-saccharide, such as ribose, galactose, glucose, or mannose.

A second embodiment relates to the design, synthesis, and evaluation of novel prodrugs that are derivatives of cysteamine or selenocysteamine, such as of WR compounds, particularly WR-1065. The prodrug strategy is similar to that employed for L-cysteine, using a protecting group R'. R' is typically a sugar, such as ribose. The modified WR prodrugs have numerous uses including protection against the side effects of radiation and chemotherapy, radiation and chemical induced mutations, such as from

exposure to radiation during a nuclear accident or chemical spill, and even spontaneous mutations which are the cause of most cancers.

These prodrugs can be described by the formula:



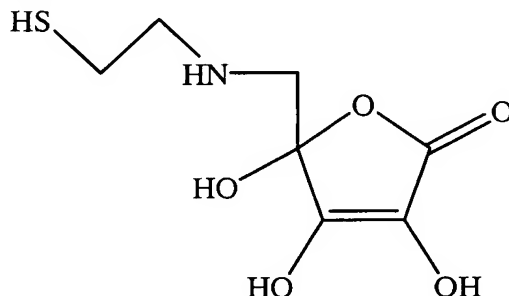
5 where A is sulfur or selenium, R' is derived from a sugar and has the formula $(\text{CHOH})_n\text{CH}_2\text{OH}$, where n is 1 to 5. R' may also be hydrogen, an alkyl or aryl group, such as methyl, ethyl, benzyl, carboxyl, polyhydroxyalkyl, or phenyl, or may also be =O. The R'' groups may be the same or different and may be alkyl, alkoxy, or carboxy, such as acetyl, methyl, or ethyl.

10 These novel thio- and selenol-containing compounds overcome several problems facing the art, including toxicity, water-solubility, and lack of target specificity. First, the protective or preventive activity and clinical utility will be greatly enhanced by converting the cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and WR compounds to thiazolidine and selenazolidine prodrug forms. These prodrugs provide a
15 slow release form of the thiol-/selenol-amine, which greatly reduces observed toxicity (with related compounds), but provides the active agent after enzymatic or non-enzymatic biotransformation

In a third embodiment, the invention relates to the design, synthesis, and evaluation of novel covalent conjugates of thiolamines or selenolamines and antioxidant
20 vitamins, e.g., Vitamin E and Vitamin C. These compounds include conjugates of any of the prodrug compounds of the invention defined above conjugated with Vitamin C or Vitamin E. Also contemplated by the invention are conjugates of antioxidant vitamins

with the following thiol- and selenol-amines and derivatives thereof; cysteine, cystine, cysteamine, cystamine, glutathione, selenocysteine, selenocysteamine, selenocystine, selenocystamine, and WR compounds (WR-1065 and WR-33278).

An example, shown below, is a conjugate of cysteamine and Vitamin C.

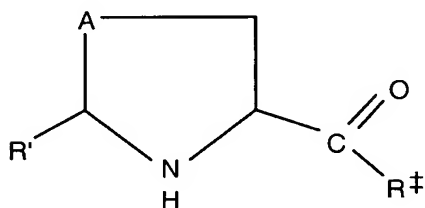


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These compounds are effective because protective or preventive treatment of toxic insults will be far more effective if thiol- or selenol-containing compounds are delivered together with antioxidants such as vitamin C and E, which also play a protective and preventive action in the body. The complementary mechanisms of these compounds would increase the overall effectiveness of treatment.

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In yet another embodiment, the invention relates to the design, synthesis, and evaluation of novel L-cystein and L-selenocysteine prodrugs which have been modified with ester or amine groups at the carboxylic acid position. These can be described by formula:

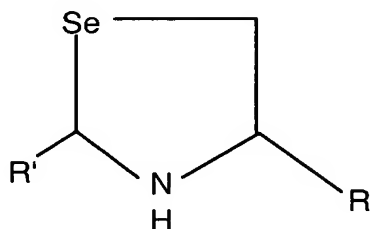


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where A is sulfur or selenium, and R' is derived from a sugar and has the formula $(\text{CHOH})_n\text{CH}_2\text{OH}$, where n is 1 to 5. R' may also be an alkyl or aryl group, such as methyl, ethyl, benzyl, carboxyl, or phenyl, or may also be =O. R^+ is an alkoxy, such as $-\text{OR}^1$, where R^1 is ethyl or methyl. R^+ may also be an amine group $(-\text{NR}^{\dagger}_2)$, where the R^{\dagger} groups are the same or different and can be hydrogen or an alkyl group, such as methyl.

20

Yet another embodiment of the invention is the condensation product of a selenolamine and a carbonyl donor characterized by the formula:



where R is COOH (prodrug of L-selenocysteine) or is H (prodrug of selenocysteamine).

- 5 R' is derived from a sugar and has the structure $(\text{CHOH})_n\text{CH}_2\text{OH}$, and where n is 1 to 5; or R' is an alkyl or aryl group, such as methyl, ethyl, benzyl, carboxyl or phenyl; or R' is =O.

DETAILED DESCRIPTION OF THE INVENTION

I. Thioglycoside Prodrugs

10 1. Agent Design

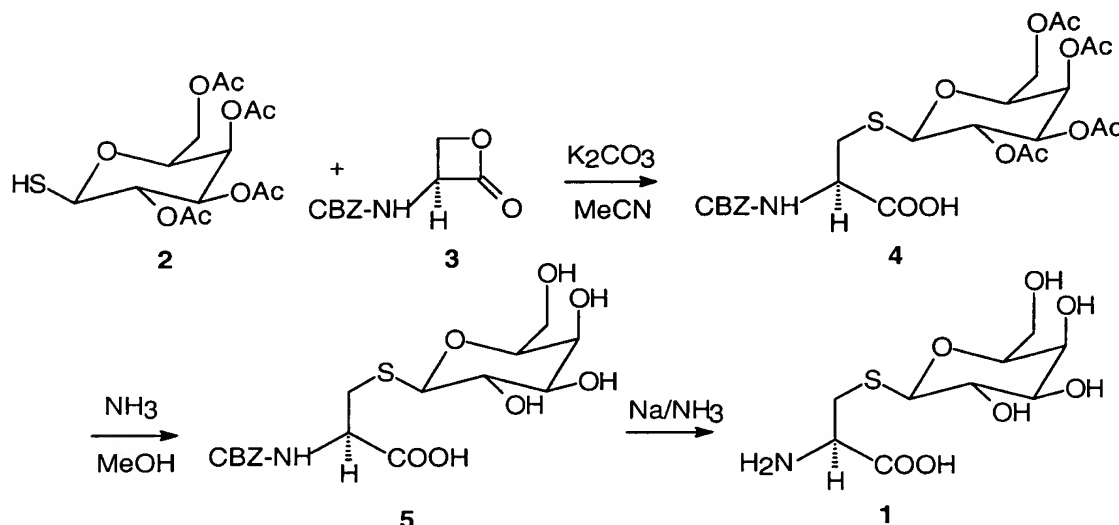
Prodrugs of L-cysteine and L-selenocysteine containing a thioglycoside or selenoglycoside on the free thiol or selenol can be prepared. The protecting group will, in addition to protecting the thiol or selenol from oxidation, permit the targeting of specific sites within the body.

- 15 For example, a galactose protected cysteine will target the liver and will enter the cytoplasm of hepatocytes. Delivering L-cysteine to hepatocytes has numerous uses, including protection against hepatotoxins, such as acetaminophen, and against side effects caused by local radiation treatments.

2. Chemical Synthesis.

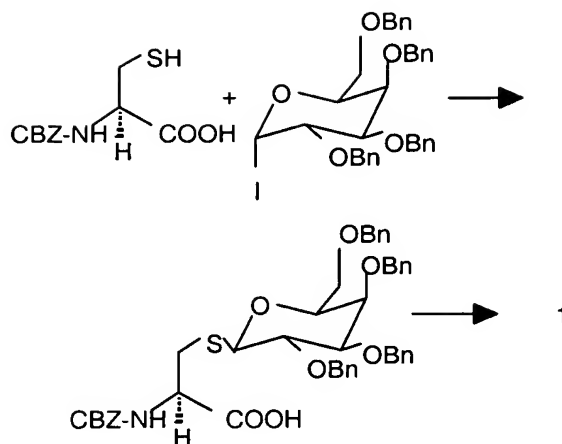
- 20 The prodrug of L-cysteine (compound 1) was prepared as shown in Scheme 1. The protected thiogalactose analog 2 was alkylated with L-serine beta-lactone 3 in the presence of potassium carbonate. The protected thiopyranoside 4 was isolated in 70%

yield after purification by silica gel chromatography. The acetate protecting groups were removed by treatment of 4 with methanolic ammonia, giving 5. Sodium in liquid ammonia was then used to remove the amino protecting groups, giving the target prodrug 1.



Scheme I

An alternative route to prodrug 1 features the formation of the thiopyranoside bond by displacement of iodine from a suitably protected galactosyl iodide (Scheme II). This route would eliminate the need to prepare β -lactone 3 (the purification of which is difficult and not very versatile with respect to the range of α -amino protecting groups that can be used) and makes it possible to use hydroxyl (on the sugar) and amino (on the cysteine) protecting groups that can be removed in a single reaction to generate the target compound 1.



Scheme II

II. Thiazolidine Prodrugs of Walter Reed (WR) Compounds

1. Agent Design

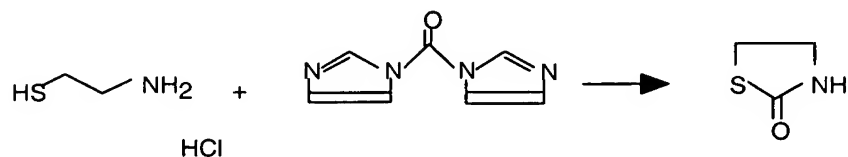
- Thiazolidine prodrug forms can be prepared from the thiolamine and virtually any carbonyl-containing compound, particularly sugars, such as the aldose monosaccharide, D-ribose, as an aldehyde that results in thiazolidines with superior protective activity. Numerous sugars or alkyl/aryl aldehydes or ketones can be used. These product thiazolidines will undergo non-enzymatic dissociation to liberate the active thiolamine. In addition, the 2-oxo derivatives can be prepared, which require enzymatic action to liberate the active thiolamine.

2. Chemical Synthesis

- a. 2-Thiazolidinone (prodrug of cysteamine and starting material for other syntheses)

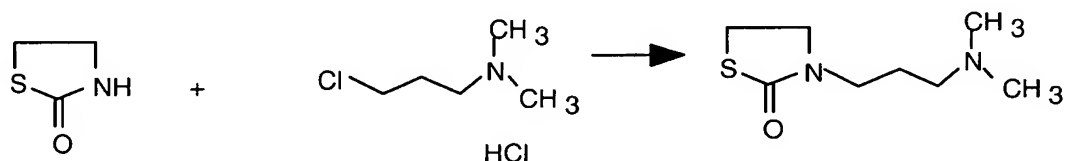
- Carbonyl diimidazole (15.75 g 0.097 mol) was dissolved, with heating, in 150 mL acetonitrile, which has been degassed and flushed with nitrogen. To this was added, cysteamine hydrochloride (10.01 g, 0.088 mol), potassium carbonate (13.50 g, 0.098 mol), and 18-crown-6 (catalytic amount), and the solution was stirred at reflux ($\sim 80^\circ\text{C}$)

for 19 hours. After this time, solvent was removed in vacuo. The crude product was redissolved in 100 mL 5% sodium carbonate and refluxed for 1 hour, then acidified to pH 2 with concentrated hydrochloric acid. The resulting solid was removed via filtration and the product was extracted from the filtrate into ethyl acetate (12 x 35 mL). The combined organic portion was washed with 1 M potassium chloride and saturated sodium chloride (50 mL each), dried over sodium sulfate, filtered, and dried in vacuo. Yield was 3.8 g, 42%.



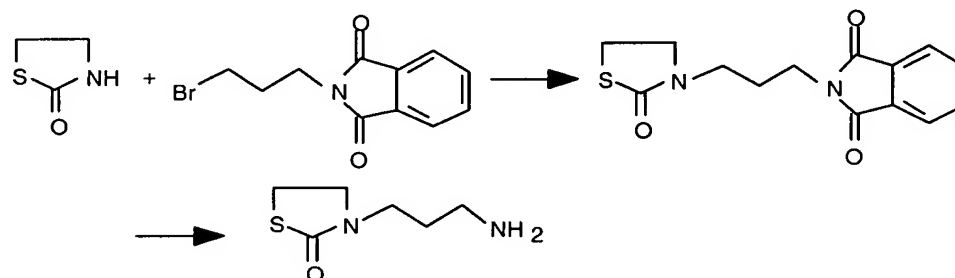
b. (N',N'-Dimethyl-3-aminopropyl)-2-thiazolidinone

To a solution of 2-thiazolidinone (4.15 g, 40.18 mmol) in acetonitrile (60 mL) were added potassium carbonate (13.3 g 96.2 mmol), N,N-dimethyl-3-aminopropyl chloride hydrochloride (7.63 g, 48.3 mmol), and 18-crown-6 (catalytic amount). The mixture was refluxed for 18 hours, solvent removed in vacuo, then redissolved in dichloromethane and 1 M potassium chloride (40 mL each). The aqueous phase was isolated and extracted twice with 30 mL portions of dichloromethane. The combined organic fraction was washed with saturated sodium chloride (~50 mL), dried over sodium sulfate, filtered, and dried in vacuo. The crude product was purified via silica gel chromatography, using a 10:1 ratio of silica gel A, 200-425 mesh, and eluting with 5% methanol in chloroform, yielding 1.15 g (15%) pure product.



c. *3-(3[]-Aminopropyl)-2-thiazolidinone*

To a solution of 2-thiazolidinone (0.994 g, 9.64 mmol) in acetonitrile (10 mL) were added N-phthalimido-3-bromopropylamine (2.88 g, 10.7 mmol), potassium carbonate (1.64 g, 11.9 mmol), and 18-crown-6 (catalytic amount). The mixture was
5 refluxed about 17 hours, solvent was removed in vacuo, and the resulting solid was redissolved in 1 M potassium chloride and dichloromethane (~25 mL each). The aqueous phase was separated and extracted with 2 x 25 mL dichloromethane. The combined organic fraction was dried over sodium sulfate, filtered, and dried in vacuo. The crude product was recrystallized from acetone/methanol to give 1.54 g (55% yield). To a
10 warmed solution of the phthalimido protected amine (1.53 g, 5.27 mmol) in 6:1 isopropanol:water was added sodium borohydride (1.01 g, 26.7 mmol), and the mixture was stirred at 60°C for 22 hours. Glacial acetic acid (5.4 mL) was added, and the solution was stirred at 80°C for 2 hours, then the solution was cooled and dried in vacuo. The product was redissolved in 6 N hydrochloric acid, washed with ether (2 x 30 mL), then
15 dried in vacuo. The product was purified via recrystallization from hot water.



Similar procedures are employed to produce the terminal monomethylated form, as well as the terminal N-acetyl compound. In addition, various allyl or aryl aldehydes or ketones are employed to produce the corresponding allyl or aryl substituent at the 2
20 position, as opposed to the 2-oxo derivatives presented above.

Radioprotection in *E. coli* AB1157

A well characterized bacterial system was used as an initial screen for radioprotective activity of the novel compounds. A single colony of the bacteria, growing

on a plate of LB medium (10 g tryptone, 5 g yeast extract, plus 5 g NaCl in 1 L water), was inoculated into 2 mL LB and incubated overnight. 20 mL LB medium were then inoculated with 600 µL of the overnight culture, and incubated with shaking at 37°C, 250 rpm. The cells were collected and washed with phosphate buffered saline. At this point the bacteria could be irradiated, treated with drug, etc., as outlined below. After dilution of the treated cells to 100 cells per 100 µL, they are plated out and incubated overnight. Cell viability is then measured by colony forming ability.

Growth curves were generated for the bacteria in the absence of any treatment to provide experience with basic handling as well as important baseline information. The radiation dose response of the system was investigated irradiating bacterial cultures in a Shepherd Mark I ¹³⁷Cs irradiator over a dose range of 0 to 1 kGy. The dose-response curves are linear and reproducible from day to day. From these data, a radiation dose of 0.6 kGy was chosen for the initial radioprotection experiments in order to achieve approximately a 0.1% survival in the unprotected cultures, a common target for these types of studies.

The toxicity of the compounds of interest in this system was explored. Administering the 2-oxocysteamine prodrug completely eliminated the profound toxicity observed with cysteamine itself; neither WR-1065 nor its 2-oxo prodrug produced any toxicity in this assay.

Radioprotection experiments were also conducted in the bacterial system. For these experiments, the bacteria were grown to log phase and then treated with the agent of choice (parent, prodrug, or positive control) for 1 hour before irradiation at 0.6 kGy. Surviving fraction compared to that seen in control (untreated) cells, which were not irradiated, was then calculated. The positive controls homocysteine thiolactone (HCTL) and WR-1065 showed the greatest amount of protection.

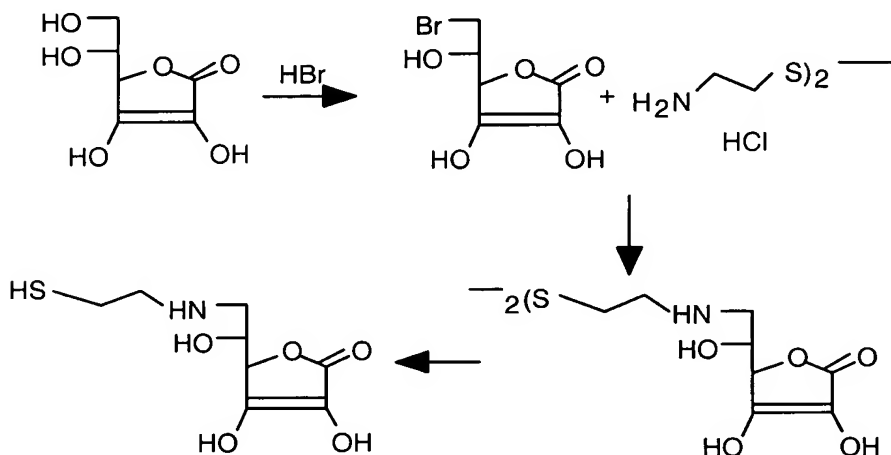
III. Covalent Conjugates of Thiol- or Selenol-amines and Antioxidant Vitamins

1. Agent Design

The present invention focuses on the antioxidant vitamins C and E, and the thiol or selenol agents, cyst(e)ine, cyst(e)amine, N-acetylcysteine, glutathione, WR-1065/WR-33278, selenocyst(e)ine, and selenocyst(e)amine. This represents a minimum of 24 combinations of the two classes. It will be appreciated by those skilled in the art that other antioxidants can be conjugated to these thiol- or selenol-containing compounds.

2. Chemical Synthesis

The schemes below summarize potential approaches using cysteamine for illustrative purposes. Many permutations are available.



IV. Modified Prodrugs of L-Cysteine or L-Selenocysteine

1. Agent Design

These prodrugs possess a modified carboxyl group compared to unmodified prodrugs of L-cysteine and L-selenocysteine. The purpose of the modification is to reduce the hydrophilicity of the prodrugs and improve their cellular uptake and retention.

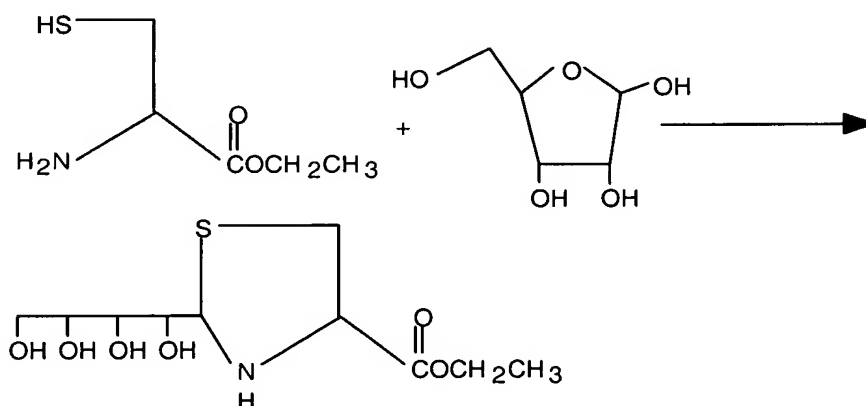
in the body. The modifications include converting the carboxyl group to an ester or amide functionality.

2. Chemical Synthesis

Ester prodrugs were prepared beginning with commercially available L-cysteine methyl or ethyl ester. The ester is combined with an equimolar amount of carbonyl donor, i.e., acetaldehyde, the aldose monosaccharide, D-ribose, or phenyl chloroformate. The amide prodrugs were prepared by the initial synthesis of L-cysteine amides (not commercially available) from L-cysteine and the appropriate amine, such as ammonia, methylamine, or dimethylamine. The synthesized L-cysteine amides were then reacted with an equimolar amount of carbonyl donor, i.e., acetaldehyde, the aldose monosaccharide, D-ribose, or phenyl chloroformate.

Modified prodrugs of L-selenocysteine can be constructed in an identical fashion. However, L-selenocysteine methyl or ethyl ester are prepared by the esterification of L-selenocysteine with methanol or ethanol because these compounds are not commercially available.

For example, the reaction of L-cysteine ethyl ester and D-ribose may be as follows;



V. Selenazolidines: Modified Prodrugs of Selenocysteine and Selenocysteamine

1. Agent Design

Current selenium supplements rely on inorganic forms. While these forms have some value, they are considered more toxic than necessary, and are unlikely to be useful in cancer chemoprevention or in AIDS supplementation. Several organoselenium compounds, which appear to be less toxic in general than the inorganic forms, have been proposed for in vivo use, but the full potential of this strategy has not yet been realized. In general, however, it is very clear that the chemical form in which selenium is introduced consistently shows a marked influence on biological outcomes.

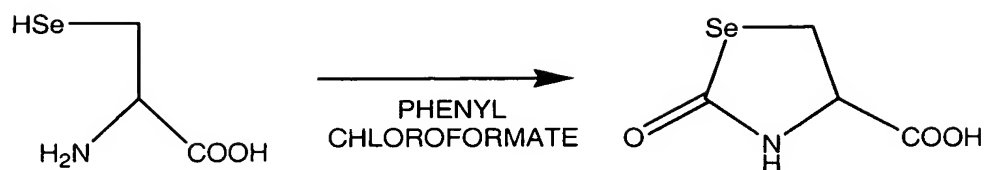
Selenocysteine is an organic form that is present in the body and is now recognized as the 21st amino acid used in protein synthesis. Due to its differential metabolism, it represents the biochemically superior form in which to supply the body with selenium.

Unfortunately, selenocysteine is chemically unstable and difficult to handle. Therefore, prodrug forms of the amino acid have been designed which represent chemically superior forms. Similar arguments hold for selenocysteamine as well.

2. Chemical Synthesis

Selenocysteine/selenocysteamine prodrugs can be synthesized by the chemical condensation of the selenolamine with a carbonyl donor. Alkyl or aryl aldehydes or ketones can be used, including simple donors such as acetaldehyde or benzaldehyde, or aldose or ketose mono- or di-saccharides. In addition, carbonyl donors such as phenyl chloroformate can be used to produce 2-oxo derivatives.

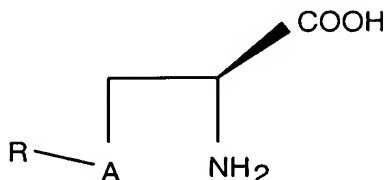
For example, the reaction of L-selenocysteine and phenyl chloroformate is illustrated.



While this invention has been described with reference to certain specific
embodiments and examples, it will be recognized by those skilled in the art that many
variations are possible without departing from the scope and spirit of this invention, and
5 that the invention, as described by the claims, is intended to cover all changes and
modifications of the invention which do not depart from the spirit of the invention.

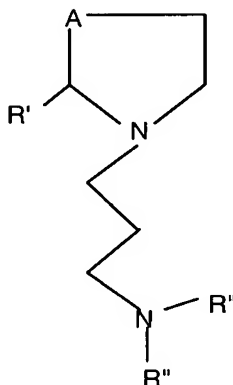
ABSTRACT OF THE DISCLOSURE

Disclosed is a prodrug of the formula:



where A is a sulfur or a selenium, and R is derived from a mono-, di-, or oligo-saccharide.

Also disclosed is a prodrug of the formula:



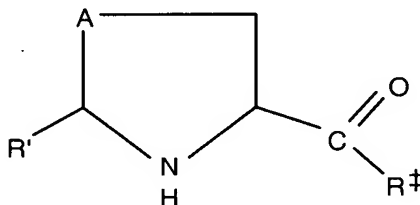
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where A is sulfur or selenium, R' is derived from a sugar and R' has the formula $(\text{CHOH})_n\text{CH}_2\text{OH}$, where n is 1 to 5, or R' is an alkyl or aryl group, or R' is =O, and the R'' groups may be the same or different and may be hydrogen, alkyl, alkoxy, or carboxy.

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Also disclosed is a conjugate of an antioxidant vitamin and a thiolamine or selenolamine.

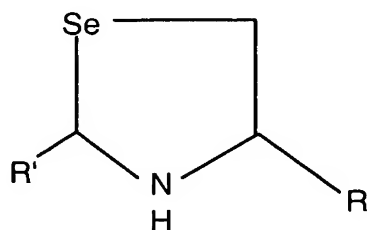
Also disclosed is a prodrug of the formula:



where A is sulfur or selenium, and R' is derived from a sugar and R' has the formula

$(\text{CHOH})_n\text{CH}_2\text{OH}$, where n is 1 to 5, or R' is also an alkyl or aryl group, or R' is $=\text{O}$, and R^+ is an alkoxy or an amine group.

Also disclosed is a prodrug of the formula:



- 5 where R is COOH or H , and R' is derived from a sugar and R' has the formula $(\text{CHOH})_n\text{CH}_2\text{OH}$, where n is 1 to 5, or R' is an alkyl or aryl group, or R' is $=\text{O}$.